How Useful is Pulse Oximetry for Screening of Congenital Heart Disease in Newborns?

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SUMMARY

In the initial pilot study at three hospitals in Shanghai, the authors assessed the accuracy of pulse oximetry plus clinical assessment for detection of congenital heart disease. They then undertook a large, prospective, and multicenter screening study in all consecutive neonates (aged 6–72 h) born at 18 hospitals in China between August 1, 2011, and November 30, 2012. Newborns with positive screen results (either an abnormal pulse oximetry or abnormal clinical assessment) were referred for echocardiography within 24 h of screening. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios for pulse oximetry alone, and in combination with clinical assessment, for detection of major and critical congenital heart disease were calculated.

In the pilot study, 6785 consecutive newborns were screened; 46 of 49 cases of asymptomatic major congenital heart disease and eight of eight cases of asymptomatic critical disease were detected by pulse oximetry and clinical assessment. In the prospective multicenter study, they screened 122 738 consecutive new born babies (120 707 asymptomatic and 2031 symptomatic), and detected congenital heart disease in 1071 (157 critical and 330 major). In asymptomatic newborns, the sensitivity of pulse oximetry plus clinical assessment was 93·2% (95% CI 87·9–96·2) for critical congenital heart disease and 90·2% (86·4–93·0) for major disease. The addition of pulse oximetry to clinical assessment improved sensitivity for detection of critical congenital heart disease from 77·4% (95% CI 70·0–83·4) to 93·2% (87·9–96·2). The false-positive rate for detection of critical disease was 2·7% (3298 of 120 392) for clinical assessment alone and 0·3% (394 of 120 561) for pulse oximetry alone.

The authors concluded that pulse oximetry plus clinical assessment is feasible and reliable for the detection of major congenital heart disease in newborns in China. They recommended this combined method to be used in maternity hospitals to screen for congenital heart disease.

COMMENTARIES

Evidence-based-medicine Viewpoint

Relevance: Early diagnosis of congenital heart disease (CHD) is important for appropriate management of potentially critical (yet often treatable) conditions. An ideal diagnostic test is expected to be accurate, reliable, reproducible, and applicable at the point-of-care (place of birth). Echocardiography fits the bill, but is expensive, requires considerable expertise, and is not easily available at most centers. Meticulous clinical examination alone can miss cases, and is highly dependent on the observer's training, skill and experience. Further, most delivery centers do not apply a standardized protocol of newborn examination, resulting in missing congenital heart disease. Against this backdrop, the study by Zhao, *et al.* [1] appears to be of great relevance.

Critical appraisal: The study was a large prospective, multi-center investigation, screening newborn infants for CHD using clinical examination, pulse oximetry, and both (diagnostic tests). Echocardiography was performed in all asymptomatic infants who had an abnormal screen result (defined as any of the three screening tests being abnormal), as well as a smaller cohort of symptomatic infants. The investigators undertook a pilot study in three Shanghai hospitals representative of Chinese delivery centers, and enrolled over 6700 infants to confirm the feasibility of the study procedures. Thereafter all consecutively born infants (>122,000) in 18 hospitals across the country, underwent the screening tests (between 6-72 h of life). Standard definitions were used to define a positive screen. The authors analyzed asymptomatic and symptomatic infants separately. Asymptomatic babies with a negative screen were followed clinically at 6 weeks and by parental feedback, to determine if a diagnosis of congenital heart disease

TABLE I CRITICAL APPRAISAL OF THE STUDY

Validity	
Are the results of the study valid?	The investigators applied the diagnostic test (clinical examination, pulse oximetry, and the combination) in a large cohort of consecutively born infants in three hospitals. Only a few babies who were antenatally diagnosed were excluded from analysis. Thus there is very low risk of selection bias in this study.
Was the reference standard applied regardless	All newborn infants underwent the three screening tests. In the pilot study of the index test result (n=6785) all infants underwent echocardiography as the reference standard, which was performed regardless of the screening test results. However in the main study, echocardiography was performed only in those with an abnormal result and in symptomatic babies. Further, this is a passive system of detection based on parents bringing sick infants. Obviously, there is a danger that several infants (including all that died) would be missed by this method. This may explain why the investigators detected 1071 CHD among 122738 enrolled infants (0.87%) whereas the expected baseline prevalence was estimated to be 1.25-1.62%.
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	The reference test (echocardiography) used in this study is the current 'gold standard' believed to be as close to the 'truth' as possible. However, in the main study, it was performed only in 2031 symptomatic infants and asymptomatic infants with a positive screening test (exact number unclear). Diagnosis of CHD in asymptomatic infants with a negative screen was sought by clinical follow-up and parental feedback to the reference standard.
Results	
Test characteristics and measures	The authors presented the results for clinical assessment alone, pulse oximetry alone, and the combination. The specific outcomes of interest were critical CHD (fatal or requiring correction before 28d) and major CHD (critical CHD plus cases requiring intervention before 1y of age). Results for the combination are summarized below. Critical CHD: Sn=93·2% (87·9–96·2); Sp=97·1% (97·1–97·2); PPV=3·8% (3·2–4·5); NPV= 99·99% (99·98–100); LR+ = 32·6% (32·5–32·6); LR- = 0·07% (0·06–0·09) Major CHD: Sn=90·2% (86·4–93·0); Sp=97·3% (97·2–97·4); PPV=7·9% (7·1–8·9); NPV=99·97% (99·96–99·98); LR+ = 32·9% (32·9–33·0); LR- = 0·10% (0·10–0·11). The data suggest that the combination was fairly accurate, and could predict the absence of critical or major CHD reliably. The likelihood ratios suggest that the test could be very useful in that setting. For all parameters (except PPV), the combination performed better than either clinical examination or pulse oximetry alone.
Applicability	
Do the methods described permit replication?	The investigators have provided detailed descriptions of the clinical examination protocol which included four indicators (family history of CHD, special facial characteristics, cardiac murmur after the first day, and non-cardiac malformations). Likewise, the method and device for pulse oximetry measurement are also well described. Overall, the diagnostic test appears applicable in diverse settings. Successful pilot testing in a few thousand infants before initiating the study confirmed the replicability of the procedures and results. However, the diagnostic test was applied at 6-72h of age; whereas cardiac murmur was considered only after 24 h; this apparent discrepancy is not elaborated by the authors. There is no description of the accuracy, reliability and reproducibility of the pulse oximeters used in this study.

LR- = Likelihood ratio of a positive test, LR- = Likelihood ratio of a negative test, NPV=Negative predictive value. Sn=Sensitivity, SP=Specificity, PPV=Positive predictive value.

emerged. However all symptomatic infants underwent echocardiography. CHD was categorized into four groups *viz* critical, serious, significant and non-significant; the first two groups were combined as major CHD and the latter two as minor CHD. The outcome of interest was critical and major CHD. The investigators reported that the screening tests were highly sensitive and specific for detecting the outcomes of interest. The combination of clinical examination plus pulse oximetry performed better than either alone.

The study provides an opportunity to critically appraise a well-designed investigation of diagnostic test accuracy. Most tools available for the purpose [2-7] examine reports as shown in ***Table* I**. The sample size was not calculated *a priori*, but *post hoc* analysis suggested that the pilot study was adequately powered. Appropriate statistical tests were used in the study and data were presented using all parameters for diagnostic tests.

Extendibility: At first glance, the diagnostic test described in this study appears simple to use at various levels of clinical care, as in the Indian health-care delivery system. However, it should be noted that the results presented were obtained in a highly controlled research setting, wherein specially trained observers and meticulous procedures were involved. It is debatable whether such promising results would be obtained in the operational setting where deliveries are not always conducted by physicians, level of training of personnel is variable, accuracy of oximetry devices is unconfirmed, and supervision/monitoring may be limited. The other important issue is what could/should be done in the event of an abnormal test result. Most maternity facilities have no access to confirmatory echocardiography, and positive test results would obviously translate to referral. This could create unwarranted anxiety and inconvenience to families, as well as an over-burden on the limited centers with facilities for neonatal echocardiography.

Conclusions: This study suggests that meticulous clinical examination of newborn infants supplemented with pulse oximetry could be a useful diagnostic test to detect critical and major congenital heart disease in diverse clinical settings. The methods can be extended to the Indian context, although the results may be variable.

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Neonatologist's Viewpoint

Among all birth defects, CHD is single most common and important cause of infant mortality [8]. Critical congenital heart diseases consist of a subgroup which needs surgery or catheter intervention in the neonatal period [9]. Timing of manifestation of critical CHD is dependent on fall in pulmonary vascular resistance and closure of ductus arteriosus. Neonates with critical CHDs may not manifest clinical signs like murmur, tachypnea or cyanosis in first 48-72 h of birth and therefore discharged undiagnosed. Delay in detection and presentation with circulatory collapse or severe cyanosis is associated with worse outcome. In pre-symptomatic period, pulse oximetry can detect subclinical hypoxemia resulting from decreased pulmonary blood flow or intracardiac shunting. With high-quality evidence from high-resource settings demonstrating efficacy of pulse oximetry in early detection of critical CHD, many developed countries have implemented a universal pre-discharge screening program [10]. In this study [1] on a large cohort from China, pulse oximetry combined with clinical assessment was able to detect more than 90% of critical CHD. Sensitivity of clinical assessment alone was lower than pulse oximetry. Pulse oximetry was especially useful in detection of cyanotic CHD like transposition of great vessels and total anomalous venous connection. However, true benefit of screening strategy lies not in early and accurate diagnosis, but in preventing morbidity and mortality due to the target condition. The study does not present data on outcome of neonates diagnosed with the screening strategy. Early detection may not translate into survival if post-screening procedures are not in place.

Universal metabolic screening is a well-established practice in high-income countries. Despite being home to second largest population in world and therefore with potentially huge burden of metabolic disorders, no state in India has been able to introduce and sustain universal neonatal screening program. Lack of laboratory set up, trained manpower, non-availability of confirmatory tests and high-cost of treatment of metabolic disorders have precluded implementation of universal screening program in India and other low- and middle-income countries. A screening program to diagnose critical CHD needs to be assessed in this context. Equipment, training and time needed to screen and interpret results of pulse oximetry are less resource-intensive than metabolic screening. CHD are more common than most of metabolic disorders, making a pulse oximetry screening program potentially more cost-effective. However, difficulties start once an infant is labeled as 'suspect' on the basis of screening program.

1. *Availability of confirmatory test:* Suspected patients of CHD need quick confirmation by echocardiography either at site of birth or referral to a center where a trained pediatric cardiologist is available. Majority of

births occur in health facilities where pediatric cardiologist is not available. Even in centers where a cardiologist is available, the screening program can significantly increase the work-load. Pulse oximetry has high false-positivity rate resulting in large number of neonates labeled 'suspect', and therefore necessitating echocardiographic confirmation.

2. *Availability of treatment:* Early diagnosis of critical CHD is useless unless immediate palliative or corrective intervention is done. In most settings of developing world, Pediatric cardiac intervention set-ups are rarely available. Treatment needs even greater infrastructure in the form of Pediatric cardiothoracic surgeon, neonatal anesthesiologist and pediatric cardiac intensive care unit.

High-quality evidence now exists favoring role of pulse oximetry screening program in early diagnosis of critical CHD [3]. Nevertheless developing countries first need to bring down infant and neonatal mortality by implementing measures to save infants from infections, birth asphyxia and prematurity. Time-consuming process of creating a pool of trained manpower and establishing infrastructure to diagnose and manage complex birth defects like CHDs need to be started meanwhile.

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Pediatric Cardiologist's Viewpoint

CHD is an important public health issue, with an incidence of 2 to 3 cases of critical CHD per 1000 live births, and has been shown to be responsible for more than 40% of infant deaths related to congenital malformations [11,12]. Without a prenatal and postnatal screening test, even severe forms of CHD commonly go undetected on usual clinical examination until after discharge to home, leading to avoidable morbidity and mortality [13]. Prenatal or postnatal detection of major forms of CHD, may improve preoperative conditions and survival after surgery. Prenatal diagnosis is the optimum need as it offers several options, including termination of pregnancy, *in utero* treatment, and planning the timing, mode and place of delivery to a better equipped tertiary care center with facilities for cardiac surgery. However, current approaches to prenatal screening for CHD remains flawed, commonly missing more than half of the cases of severe CHD [14-16].

Routine neonatal examination fails to diagnose more than half of babies with heart disease; examination at 6 weeks misses one-third [17]. Spending more time on physical examination is unrewarding as only milder cases of pulmonic stenosis and other relatively benign forms of CHD are diagnosed, which has little impact on the morbidity and mortality from undiagnosed CHD. Pulse oximetry can pick up lesions producing low oxygen saturation levels consequent to substantial abnormal mixing of systemic and pulmonary blood streams or critical obstructive duct-dependent lesions (mostly cyanotic CHD). Although it may fail to detect acyanotic CHD and critical CHD with non-critical obstruction or mixing, these lesions do not contribute to early mortality and morbidity.

This paper expresses the sensitivity of a combination of both the physical examination and pulse oximetry over pulse oximetry alone. Improving the diagnosis of CHD by a physical examination is unrewarding as there is a poor correlation between the ease of diagnosis and the severity of the cardiac lesion [18]. However, physical examination for CHD in this study was not only based on presence of murmurs, cyanosis or congestive heart failure, but on the whole gamut of history – including family history of CHD – and examination findings, including syndromic facies and extra cardiac anomalies, thereby increasing the sensitivity and specify of picking up more of critical and major CHD. The paper does not report the competency of the pediatrician, and on the time spent to auscultate the heart.

A recent systematic review [19] of data from 229 421 new born babies reported high specificity and acceptable sensitivity for detection of critical CHD. The false-positive rate for detection of critical congenital heart defects was particularly low when new born pulse oximetry was done after 24 h from birth than when it was done before 24 h.

Although pulse oximetry is inexpensive and without side effects, it cannot detect CHD in every neonate with congenital heart disease, before they leave the hospital. Pulse oximetry is highly specific for detection of critical congenital heart defects with moderate sensitivity that meets criteria for universal screening [20]. In a country with a huge population and poor prenatal diagnostic infrastructure, it is probably the best thing to do and should become a recommendation. We still need to address several issues including overall costs of screening, delayed diagnoses because of false-negative screen results, the costs of evaluation and the iatrogenic anxiety/ fears generated in families of children with false positive screen results .

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Erratum

In article entitled "Newborn Screening for Congenital Hypothyroidism, Galactosemia and Biotinidase Deficiency in Uttar Pradesh, India", published in September 2014 issue of Indian Pediatrics on page nos. 701-5, few errors were detected after publication. The errors have now been corrected and the revised version of the manuscript has been uploaded at our website *www.indianpediatrics.net.*